

METHADONE HYDROCHLORIDE- methadone hydrochloride concentrate
Cebert Pharmaceuticals, Inc.

Methadone Hydrochloride Oral Concentrate USP, 10 mg per mL
(Dye-Free, Sugar-Free, Unflavored) and
Methadone Hydrochloride Oral Concentrate USP, 10 mg per mL
(Cherry)

FOR ORAL USE ONLY.

Rx only

CONDITIONS FOR DISTRIBUTION AND USE

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS FOR THE TREATMENT OF OPIOID ADDICTION

Code of Federal Regulations, Title 42, Sec 8

METHADONE PRODUCTS WHEN USED FOR THE TREATMENT OF OPIOID ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY OPIOID TREATMENT PROGRAMS (AND AGENCIES, PRACTITIONERS OR INSTITUTIONS BY FORMAL AGREEMENT WITH THE PROGRAM SPONSOR) CERTIFIED BY THE SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION AND APPROVED BY THE DESIGNATED STATE AUTHORITY. CERTIFIED TREATMENT PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL OPIOID TREATMENT STANDARDS (42 CFR 8.12). **See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.**

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL, AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

Regulatory Exceptions to the General Requirement for Certification to Provide Opioid Agonist Treatment:

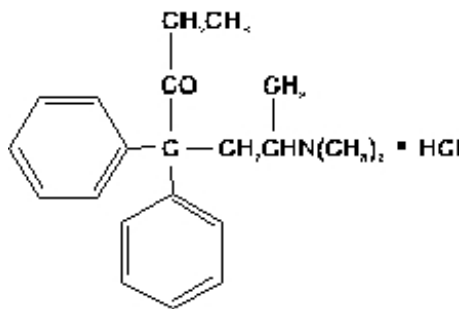
- 1. During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis.**
- 2. During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21 CFR 1306.07(b)).**

DESCRIPTION

Each mL for oral administration contains:

Methadone Hydrochloride 10 mg

Chemically, Methadone Hydrochloride is 3-Heptanone, 6-(dimethylamino)-4,4-diphenyl-, hydrochloride, which can be represented by the following structural formula:



$C_{21}H_{27}NO \cdot HCl$ M.W. 345.91

Methadone hydrochloride is a white, essentially odorless, bitter-tasting crystalline powder. It is very soluble in water, soluble in isopropranolol and in chloroform, and practically insoluble in ether and in glycerine. It is present in Methadone Hydrochloride Oral Concentrate as the racemic mixture.

Methadone hydrochloride has a melting point of 235°C, a pKa of 8.25 in water at 20°C, a solution (1 in 100) pH between 4.5 and 6.5, a partition coefficient of 117 at pH 7.4 in octanol/water.

Each mL of the unflavored liquid concentrate, for oral administration, contains 10 mg of methadone hydrochloride. Inactive ingredients: citric acid, sodium benzoate and water.

Each mL of the cherry-flavored liquid concentrate, for oral administration, contains 10 mg of methadone hydrochloride. Inactive ingredients: citric acid, D&C Red #33, FD&C Red #40, flavor, glycerin, propylene glycol, sodium benzoate, sodium saccharin, sorbitol, sucrose and water.

CLINICAL PHARMACOLOGY

Mechanism of Action

Methadone hydrochloride is a μ agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

Pharmacokinetics

Absorption

Following oral administration the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 to 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution

Methadone is a lipophilic drug and the steady state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to α_1 -acid glycoprotein (85% to 90%). Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

Metabolism

Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, and CYP2C19 and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in urine.

Excretion

The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. After multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 to 126 L/h and the terminal half-life ($T_{1/2}$) ranged between 7 to 59 hours. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

Pharmacokinetics in Special Populations

Pregnancy

There are no pharmacokinetic studies of *parenteral* methadone in pregnancy. The disposition of *oral* methadone has been studied in approximately 30 pregnant patients in 2nd and 3rd trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during second and third trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone. (See PRECAUTIONS: Pregnancy, Labor and Delivery and DOSAGE AND ADMINISTRATION.)

Renal Impairment

Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency. Unmetabolized methadone and its metabolites are excreted in urine to a variable degree. Methadone is a basic ($pK_a=9.2$) compound and the pH of the urinary tract can alter its disposition in plasma. Urine acidification has been shown to increase renal elimination of methadone. Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for increasing methadone or metabolite elimination.

Hepatic Impairment

Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways, therefore patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender

The pharmacokinetics of methadone have not been evaluated for gender specificity.

Race

The pharmacokinetics of methadone have not been evaluated for race specificity.

Geriatric

The pharmacokinetics of methadone have not been evaluated in the geriatric population.

Pediatric

The pharmacokinetics of methadone have not been evaluated in the pediatric population.

Drug Interactions

(See PRECAUTIONS, Drug Interactions.)

Methadone undergoes hepatic N-demethylation by cytochrome P-450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with inhibitors may reduce metabolism and potentiate methadone's effects. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential. Clinicians are advised to evaluate individual response to drug therapy.

INDICATIONS AND USAGE

1. Detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
2. Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

NOTE

Outpatient maintenance and outpatient detoxification treatment may be provided only by Opioid Treatment Programs (OTPs) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). This does not preclude the maintenance treatment of a patient with concurrent opioid addiction who is hospitalized for conditions other than opioid addiction and who requires temporary maintenance during the critical period of his/her stay, or of a patient whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

CONTRAINDICATIONS

Methadone Hydrochloride Oral Concentrate is contraindicated in patients with a known hypersensitivity to methadone hydrochloride or any other ingredient in Methadone Hydrochloride Oral Concentrate.

Methadone Hydrochloride Oral Concentrate is contraindicated in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia.

WARNINGS

Methadone Hydrochloride Oral Concentrate is for oral administration only. The preparation must not be injected. Methadone Hydrochloride Oral Concentrate, if dispensed, should be packaged in child-resistant containers and kept out of reach of children to prevent accidental ingestion.

Cardiac Conduction Effects

This information is provided to alert the prescribing physician, and is not intended to deter the appropriate use of methadone in patients with a history of cardiac disease.

Laboratory studies, both *in vivo* and *in vitro*, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 200 mg/day). Although most cases involve patients being treated for pain with large, multiple daily doses of methadone, cases

have been reported in patients receiving doses commonly used in maintenance treatment of opioid addiction. In most of the cases seen at typical maintenance doses, concomitant medications and/or clinical conditions such as hypokalemia are noted as contributing factors. However, the evidence strongly suggests that methadone possesses the potential for adverse cardiac conduction effects in some patients.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction disease, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increased risk of dysrhythmia. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities, and drugs which might act as inhibitors of methadone metabolism. The potential risks of methadone, including the risk of life-threatening arrhythmias, should be weighed against the risks of discontinuing methadone treatment. In the patient being treated for opiate dependence with methadone maintenance therapy, these risks include a very high likelihood of relapse to illicit drug use following methadone discontinuation.

The use of methadone in patients already known to have a prolonged QT interval has not been systematically studied. The potential risks of methadone should be weighed against the substantial morbidity and mortality associated with untreated opioid addiction.

Respiratory Depression

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Respiratory depression is of particular concern in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Methadone Hydrochloride Oral Concentrate should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, and CNS depression or coma. In these patients, even usual therapeutic doses of methadone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Alternative, non-opioid analgesics should be considered, and methadone should be employed only under careful medical supervision at the lowest effective dose.

Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, in the short-term use setting. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

Incomplete Cross-tolerance between Methadone and other Opioids

Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is of particular concern for patients tolerant to other μ -opioid agonists who are being converted to methadone, thus making determination of dosing during opioid conversion complex. Deaths have been reported during conversion from chronic, high-dose treatment with other opioid agonists. A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise.

Misuse, Abuse, and Diversion of Opioids

Methadone is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.

Methadone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be

considered when dispensing Methadone Hydrochloride Oral Concentrate in situations where the clinician is concerned about an increased risk of misuse, abuse, or diversion.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with other CNS Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with methadone may experience respiratory depression, hypotension, profound sedation, or coma (see PRECAUTIONS).

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Deaths associated with illicit use of methadone frequently have involved concomitant benzodiazepine abuse.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce effects which may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution, and only if it is deemed essential.

Acute Abdominal Conditions

The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Hypotensive Effect

The administration of methadone may result in severe hypotension in patients whose ability to maintain normal blood pressure is compromised (e.g., severe volume depletion).

PRECAUTIONS

Methadone Hydrochloride Oral Concentrate should be used with caution in elderly and debilitated patients; patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and in patients with comorbid conditions or concomitant medications which may predispose to dysrhythmia or reduced ventilatory drive.

Drug Interactions

In vitro results suggest that methadone undergoes hepatic N-demethylation by cytochrome P450 enzymes, principally CYP3A4, CYP2B6, CYP2C19 and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in a more rapid metabolism and potential for decreased effects of methadone, whereas administration with inhibitors may reduce metabolism and potentiate methadone's effects. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy.

Opioid Antagonists, Mixed Agonist/Antagonists, and Partial Agonists

As with other μ -agonists, patients maintained on methadone may experience withdrawal symptoms when given these agents. Examples of such agents are naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine.

Anti-retroviral Agents

Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination

Coadministration of these anti-retroviral agents resulted in increased clearance or decrease plasma levels of methadone. Methadone-maintained patients beginning treatment with above antiretroviral drugs should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly.

Didanosine and Stavudine

Experimental evidence demonstrated that methadone decreased the AUC and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

Zidovudine

Experimental evidence demonstrated that methadone increased the area under the concentration-time curve (AUC) of zidovudine which could result in toxic effects.

Cytochrome P450 Inducers

Methadone-maintained patients beginning treatment with CYP3A4 inducers should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly. The following drug interactions were reported following coadministration of methadone with inducers of cytochrome P450 enzymes:

Rifampin

In patients well-stabilized on methadone, concomitant administration of rifampin resulted in a marked reduction in serum methadone levels and a concurrent appearance of withdrawal symptoms.

Phenytoin

In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg b.i.d. initially for 1 day followed by 300 mg QD for 3 to 4 days) resulted in an approximately 50% reduction in methadone exposure and withdrawal symptoms occurred concurrently. Upon discontinuation of phenytoin, the incidence of withdrawal symptoms decreased and methadone exposure increased to a level comparable to that prior to phenytoin administration.

St. John's Wort, Phenobarbital, Carbamazepine

Administration of methadone along with other CYP3A4 inducers may result in withdrawal symptoms.

Cytochrome P450 Inhibitors

Since the metabolism of methadone is mediated primarily by CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone. The expected clinical results would be increased or prolonged opioid effects. Thus, methadone-treated patients coadministered strong inhibitors of CYP3A4 such asazole antifungal agents (e.g., ketoconazole) with methadone should be carefully monitored and dosage adjustment should be undertaken if warranted. Some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine) may increase methadone plasma levels upon coadministration with methadone and result in increased opiate effects and/or toxicity.

Voriconazole

Repeat dose administration of oral voriconazole (400mg Q12h for 1 day, then 200mg Q12h for 4 days) increased the C_{max} and AUC of R-methadone by 31% and 47%, respectively, in subjects receiving a

methadone maintenance dose (30 to 100 mg QD). The C_{max} and AUC of (S)-methadone increased by 65% and 103%, respectively. Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.

Others

Monoamine Oxidase (MAO) Inhibitors

Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone. However, if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small, incremental doses of methadone are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Desipramine

Blood levels of desipramine have increased with concurrent methadone administration.

Potentially Arrhythmogenic Agents

Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Caution should also be exercised when prescribing Methadone Hydrochloride Oral Concentrate concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids or CNS depressants, or with illicit drugs that cause central nervous system depression. Deaths have been reported when methadone has been abused in conjunction with benzodiazepines.

Anxiety

Since methadone as used by tolerant subjects at a constant maintenance dosage does not act as a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dose of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic withdrawal symptoms and is ineffective for relief of general anxiety.

Acute Pain

Maintenance patients on a stable dose of methadone who experience physical trauma, postoperative pain or other acute pain cannot be expected to derive analgesia from their ongoing dose of methadone. Such patients should be administered analgesics, including opioids, in doses that would otherwise be indicated for non-methadone-treated patients with similar painful conditions. Due to the opioid tolerance induced by methadone, when opioids are required for management of acute pain in methadone patients, somewhat higher and/or more frequent doses will often be required than would be the case for non-tolerant patients.

Physical Dependence

Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence is expected during opioid agonist therapy of opioid addiction.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see DOSAGE AND ADMINISTRATION: For Medically Supervised Withdrawal After a Period of Maintenance Treatment).

Special-Risk Patients

Methadone should be given with caution, and the initial dose reduced, in certain patients such as the elderly and debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression requires added vigilance.

Information for Patients

- Patients should be cautioned that methadone, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery.
- Patients should be cautioned that methadone, like other opioids, may produce orthostatic hypotension in ambulatory patients.
- Patients should be cautioned that alcohol and other CNS depressants may produce an additive CNS depression when taken with this product and should be avoided.
- Patients should be instructed to seek medical attention immediately if they experience symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, or syncope) when taking Methadone Hydrochloride Oral Concentrate.
- Patients initiating treatment with methadone should be reassured that the dose of methadone will "hold" for longer periods of time as treatment progresses.
- Patients seeking to discontinue treatment should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The results of carcinogenicity assessment in B6C2F1 mice and Fischer 344 rats following dietary administration of two doses of methadone HCl have been published. Mice consumed 15 mg/kg/day or 60 mg/kg/day methadone for two years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day on a body surface area basis (mg/m^2). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 28 mg/kg/day of methadone for two years. These doses were approximately 1.3 and 2.3 times a human daily oral dose of 120 mg/day, based on body surface area comparison. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for two years. These doses were approximately 3.7 and 7.1 times a human daily oral dose of 120 mg/day, based on body surface area comparison. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

Mutagenesis

There are several published reports on the potential genetic toxicity of methadone. Methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of *Drosophila* using feeding and injection procedures. In contrast, methadone tested positive in the *in vivo* mouse dominant lethal assay and the *in vivo* mammalian spermatogonial chromosome aberration test. Additionally, methadone tested positive in the *E.coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays.

Fertility

Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals. In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported. Published animal studies provide additional data indicating that methadone treatment of males can alter reproductive function. Methadone produces a significant regression of sex accessory organs and testes of male mice and rats. Additional data have been published indicating that methadone treatment of male rats (once a day for three consecutive days) increased embryoletality and neonatal mortality. Examination of uterine contents of methadone-naive female mice bred to methadone-treated mice indicated that methadone treatment produced an increase in the rate of preimplantation deaths in all post-meiotic states.

Pregnancy

Teratogenic Effects – Pregnancy Category C.

There are no controlled studies of methadone use in pregnant women. However, an expert review of published data on experiences with methadone use during pregnancy by the Teratogen Information System (TERIS) concluded that maternal use of methadone during pregnancy as part of a supervised, therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as “limited to fair”). However, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002). Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care leading to significantly reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality. Several factors complicate the interpretation of investigations of the children of women who take methadone during pregnancy. These include the maternal use of illicit drugs, other maternal factors such as nutrition, infection, and psychosocial circumstances, limited information regarding dose and duration of methadone use during pregnancy, and the fact that most maternal exposure appears to occur after the first trimester of pregnancy. Reported studies have generally compared the benefit of methadone to the risk of untreated addiction to illicit drugs.

Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine.

A retrospective series of 101 pregnant, opiate-dependent women who underwent inpatient opiate detoxification with methadone did not demonstrate any increased risk of miscarriage in the 2nd trimester or premature delivery in the 3rd trimester.

Several studies have suggested that infants born to narcotic-addicted women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. This growth deficit does not appear to persist into later childhood. However, children born to women treated with methadone during pregnancy have been shown to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests.

Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Additional information on the potential risks of methadone may be derived from animal data. Methadone

does not appear to be teratogenic in the rat or rabbit models. However, following large doses, methadone produced teratogenic effects in the guinea pig, hamster and mouse. One published study in pregnant hamsters indicated that a single subcutaneous dose of methadone ranging from 31 to 185 mg/kg (the 31 mg/kg dose is approximately 2 times a human daily oral dose of 120 mg/day on a mg/m² basis) on day 8 of gestation resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting congenital malformations described as exencephaly, cranioschisis, and “various other lesions.” The majority of the doses tested also resulted in maternal death. In another study, a single subcutaneous dose of 22 to 24 mg/kg methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m² basis) administered on day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effects were reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m² basis) administered during days 6 to 15 and 6 to 18, respectively.

Nonteratogenic Effects

Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent. Onset of withdrawal symptoms in infants is usually in the first days after birth. Withdrawal signs in the newborn include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the maternal dose or the duration of maternal exposure. The duration of the withdrawal signs may vary from a few days to weeks or even months. There is no consensus on the appropriate management of infant withdrawal.

There are conflicting reports on whether SIDS occurs with an increased incidence in infants born to women treated with methadone during pregnancy.

Abnormal fetal nonstress tests (NSTs) have been reported to occur more frequently when the test is performed 1 to 2 hours after a maintenance dose of methadone in late pregnancy compared to controls.

Published animal data have reported increased neonatal mortality in the offspring of male rodents that were treated with methadone prior to mating. In these studies, the female rodents were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naïve females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights. Further, behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model. Other animal studies have reported that perinatal exposure to opioids including methadone alters neuronal development and behavior in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociceptive responses and sensitivity to drugs. Additional animal data demonstrates evidence for neurochemical changes in the brains of methadone-treated offspring, including changes to the cholinergic, dopaminergic, noradrenergic and serotonergic systems. Additional studies demonstrated that methadone treatment of male rats for 21 to 32 days prior to mating with methadone-naïve females did not produce any adverse effects, suggesting that prolonged methadone treatment of the male rat resulted in tolerance to the developmental toxicities noted in the progeny. Mechanistic studies in this rat model suggest that the developmental effects of “paternal” methadone on the progeny appear to be due to decreased testosterone production. These animal data mirror the reported clinical findings of decreased testosterone levels in human males on methadone maintenance therapy for opioid addiction and in males receiving chronic intraspinal opioids.

Clinical Pharmacology

Pregnant women appear to have significantly lower trough plasma methadone concentrations, increased plasma methadone clearance, and shorter methadone half-life than after delivery. Dosage adjustment

using higher doses or administering the daily dose in divided doses may be necessary in pregnant women treated with Methadone Hydrochloride Oral Concentrate. [See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.]

Labor and Delivery

As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn. Narcotics with mixed agonist-antagonist properties should not be used for pain control during labor in patients chronically treated with methadone as they may precipitate acute withdrawal.

Methadone is secreted into human milk. The safety of breastfeeding while taking oral methadone is controversial. At maternal oral doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 µg/L in milk have been reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state. Peak methadone levels in milk occur approximately 4 to 5 hours after an oral dose. Based on an average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4 µg/kg/day which is approximately 2 to 3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone. Women on high dose methadone maintenance, who are already breast feeding, should be counseled to wean breast-feeding gradually in order to prevent neonatal abstinence syndrome.

Methadone-treated mothers considering nursing an opioid-naïve infant should be counseled regarding the presence of methadone in breast milk.

Because of the potential for serious adverse reactions in nursing infants from methadone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother, and weighing the risk of methadone against the risk of maternal illicit drug use.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Geriatric Use

Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Renal Impairment

The use of methadone has not been extensively evaluated in patients with renal insufficiency.

Hepatic Impairment

The use of methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender

The use of methadone has not been evaluated for gender specificity.

ADVERSE REACTIONS

Heroin Withdrawal

During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration

The initial methadone dose should be carefully titrated to the individual. Too rapid titration for the patient's sensitivity is more likely to produce adverse effects.

The major hazards of methadone, are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable.

Other adverse reactions include the following:

Body as a Whole: asthenia (weakness), edema, headache

Cardiovascular: arrhythmias, bigeminal rhythms, bradycardia, extrasystoles, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia, ECG abnormalities, prolonged QT interval, T-wave inversion, cardiomyopathy, flushing, heart failure, hypotension, palpitations, phlebitis, syncope

Digestive: abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Hematologic and Lymphatic: reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis

Metabolic and Nutritional: hypokalemia, hypomagnesemia, weight gain

Nervous: agitation, confusion, seizures, disorientation, dysphoria, euphoria, insomnia

Respiratory: pulmonary edema

Skin and Appendages: pruritis, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Special Senses: visual disturbances

Urogenital: antidiuretic effect, amenorrhea, urinary retention or hesitancy, reduced libido and/or potency

Maintenance on a Stabilized Dose: During prolonged administration of methadone, as in a methadone maintenance treatment program, there is usually a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.

DRUG ABUSE AND DEPENDENCE

Methadone Hydrochloride Oral Concentrate contains methadone, a potent Schedule II opioid agonist. Schedule II opioid substances, which also include hydromorphone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. **Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.**

Abuse of Methadone Hydrochloride Oral Concentrate poses a risk of overdose and death. This risk is

increased with concurrent abuse of Methadone Hydrochloride Oral Concentrate with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Since Methadone Hydrochloride Oral Concentrate may be diverted for non-medical use, careful record keeping of ordering and dispensing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Methadone Hydrochloride Oral Concentrate, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs certified by the Substance Abuse and Mental Health Services Administration (and agencies, practitioners or institutions by formal agreement with the program sponsor).

OVERDOSAGE

Signs and Symptoms

Serious overdose of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and sometimes, bradycardia and hypotension. In severe overdose, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a non-tolerant person, takes a large dose of methadone, effective opioid antagonists are available to counteract the potentially lethal respiratory depression. **The physician must remember, however, that methadone is a long-acting depressant (36 to 48 hours), whereas opioid antagonists act for much shorter periods (one to three hours).** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and may need to be treated repeatedly with the narcotic antagonist. If the diagnosis is correct and respiratory depression is due only to overdose of methadone, the use of other respiratory stimulants is not indicated.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or cardiovascular depression. In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist may precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. If antagonists must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Intravenously administered naloxone or nalmefene may be used to reverse signs of intoxication. Because of the relatively short half-life of naloxone as compared with methadone, repeated injections may be required until the status of the patient remains satisfactory. Naloxone may also be administered by continuous intravenous infusion.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

DOSAGE AND ADMINISTRATION

Methadone differs from many other opioid agonists in several important ways. Methadone's

pharmacokinetic properties, coupled with high interpatient variability in its absorption, metabolism, and relative analgesic potency, necessitate a cautious and highly individualized approach to prescribing. Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.

While methadone's duration of analgesic action (typically 4 to 8 hours) in the setting of single-dose studies approximates that of morphine, methadone's plasma elimination half-life is substantially longer than that of morphine (typically 8 to 59 hours vs. 1 to 5 hours). Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects. Also, with repeated dosing, methadone may be retained in the liver and then slowly released, prolonging the duration of action despite low plasma concentrations. For these reasons, steady-state plasma concentrations, and full analgesic effects, are usually not attained until 3 to 5 days of dosing. Additionally, incomplete cross-tolerance between μ -opioid agonists makes determination of dosing during opioid conversion complex.

The complexities associated with methadone dosing can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. **A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. Deaths have been reported during conversion to methadone from chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other agonists.**

For detoxification and maintenance of opiate dependence methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8.12, including limitations on unsupervised administration.

Induction/Initial Dosing

The initial methadone dose should be administered, under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. Initially, a single dose of 20 to 30 mg of methadone will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg. If same-day dosing adjustments are to be made, the patient should be asked to wait 2 to 4 hours for further evaluation, when peak levels have been reached. An additional 5 to 10 mg of methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose of methadone on the first day of treatment should not ordinarily exceed 40 mg. Dose adjustments should be made over the first week of treatment based on control of withdrawal symptoms at the time of expected peak activity (e.g., 2 to 4 hours after dosing). Dose adjustment should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Patients should be reminded that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.

Initial doses should be lower for patients whose tolerance is expected to be low at treatment entry. Loss of tolerance should be considered in any patient who has not taken opioids for more than 5 days. Initial doses should not be determined by previous treatment episodes or dollars spent per day on illicit drug use.

For Short-term Detoxification

For patients preferring a brief course of stabilization followed by a period of medically supervised withdrawal, it is generally recommended that the patient be titrated to a total daily dose of about 40 mg in divided doses to achieve an adequate stabilizing level. Stabilization can be continued for 2 to 3 days, after which the dose of methadone should be gradually decreased. The rate at which methadone is decreased should be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake should remain sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated. In ambulatory patients, a somewhat slower schedule may be needed.

For Maintenance Treatment

Patients in maintenance treatment should be titrated to a dose at which opioid symptoms are prevented for 24 hours, drug hunger or craving is reduced, the euphoric effects of self-administered opioids are blocked or attenuated, and the patient is tolerant to the sedative effects of methadone. Most commonly, clinical stability is achieved at doses between 80 to 120 mg/day.

For Medically Supervised Withdrawal After a Period of Maintenance Treatment

There is considerable variability in the appropriate rate of methadone taper in patients choosing medically supervised withdrawal from methadone treatment. It is generally suggested that dose reductions should be less than 10% of the established tolerance or maintenance dose, and that 10 to 14-day intervals should elapse between dose reductions. Patients should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

HOW SUPPLIED

Methadone Hydrochloride Oral Concentrate USP, 10 mg per mL

(Dye-Free, Sugar-Free, Unflavored)

Clear, flavorless solution.

NDC 64019-553-67: Bottles of 1 quart (946 mL).

Methadone Hydrochloride Oral Concentrate USP, 10 mg per mL (Cherry)

Red-colored, cherry-flavored solution.

NDC 64019-554-67: Bottles of 1 Quart (946 mL).

Store at 25°C (77°F); excursions permitted to 15°-30°C [See USP Controlled Room Temperature].

Dispense in a tight container, as defined in the USP/NF.

Protect from light.

Manufactured by: Boehringer Ingelheim Roxane, Inc., Columbus, Ohio 43216

Distributed by: Cebert Pharmaceuticals, Inc., Birmingham, Alabama 35242

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METHADONE HYDROCHLORIDE

methadone hydrochloride concentrate

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:640 19 -553
Route of Administration	ORAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METHADONE HYDROCHLORIDE (UNII: 229809935B) (METHADONE - UNII:UC6VBE7V1Z)		10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
CITRIC ACID (UNII: 2968PHW8QP)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64019-553-67	946 mL in 1 BOTTLE		

METHADONE HYDROCHLORIDE

methadone hydrochloride concentrate

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:64019-554
Route of Administration	ORAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METHADONE HYDROCHLORIDE (UNII: 229809935B) (METHADONE - UNII:UC6VBE7V1Z)		10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
CITRIC ACID (UNII: 2968PHW8QP)	
D&C Red #33 ()	
FD&C Red #40 ()	
FLAVOR ()	
GLYCERIN (UNII: PDC6A3C0OX)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
SODIUM SACCHARIN ()	
SORBITOL (UNII: 506T60A25R)	
SUCROSE (UNII: C151H8M554)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64019-554-67	946 mL in 1 BOTTLE		

